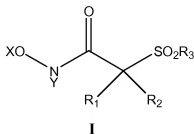


**Listing of Claims:**

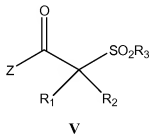
This listing of claims will replace all prior versions, and listings, of claims in the application.

1. **(Currently amended.)** A method of preparing an alpha-sulfonyl hydroxamic acid derivative of formula I,



wherein X, Y, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are defined below or a pharmaceutically acceptable salt thereof comprising:

converting a compound derivatives of the formula V:



wherein Z is H, OH, -NYOX, -OR<sub>5</sub> or -NR<sub>5</sub>R<sub>6</sub>;

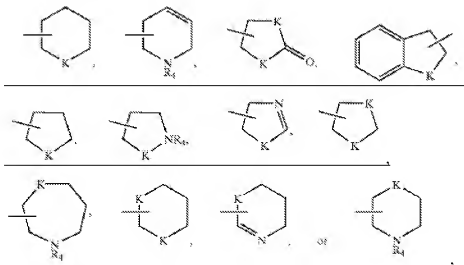
X is hydrogen, alkyl of 1-6 carbon atoms, benzyl, hydroxyethyl, t-butyltrimethylsilyl, trimethylsilyl or tetrahydropyranyl;

Y is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6 to 10 carbon atoms, 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, NR<sub>4</sub>, O and S, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl; wherein said alkyl, aryl, heteroaryl, cycloalkyl and cycloheteroalkyl group of Y is optionally substituted on any atom capable of substitution, with 1 to 3 substituents selected from the group consisting of halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, -OR<sub>5</sub>, =O, -CN, -COR<sub>5</sub>, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, -CONR<sub>5</sub>R<sub>6</sub>, -S(O)<sub>n</sub>R<sub>5</sub>, -OPO(OR<sub>5</sub>)OR<sub>6</sub>, -PO(OR<sub>5</sub>)R<sub>6</sub>, -OC(O)OR<sub>5</sub>, -OR<sub>5</sub>NR<sub>5</sub>R<sub>6</sub>, -OC(O)NR<sub>5</sub>R<sub>6</sub>, -C(O)NR<sub>5</sub>OR<sub>6</sub>, -COOR<sub>5</sub>, -SO<sub>3</sub>H, -NR<sub>5</sub>R<sub>6</sub>, -N[(CH<sub>2</sub>)<sub>2</sub>]<sub>2</sub>NR<sub>5</sub>, -NR<sub>5</sub>COR<sub>6</sub>, -NR<sub>5</sub>COOR<sub>6</sub>, SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, -NO<sub>2</sub>, -

$N(R_5)SO_2R_6$ ,  $-NR_5CONR_5R_6$ ,  $-NR_5C(=NR_6)NR_5R_6$ ,  $-NR_5C(=NR_6)N(SO_2R_5)R_6$ ,  $-NR_5C(=NR_6)NR_6N(C=OR_5)R_6$ ,  $-tetrazol-5-yl$ ,  $-SO_2NHCN$ ,  $-SO_2NHCONR_5R_6$ , phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

$R_1$  and  $R_2$  taken together with the carbon atom to which they are attached form a cycloalkyl ring of 3-8 carbon atoms or a 5-10 membered cycloheteroalkyl ring containing 1-3 heteroatoms selected from the group consisting of N,  $NR_4$ , O and S; and the cycloheteroalkyl may be optionally substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms,  $-OR_5=O$ ,  $-CN$ ,  $-COR_5$ , perfluoroalkyl of 1-4 carbon atoms,  $-O$ -perfluoroalkyl of 1-4 carbons atoms,  $-CONR_2R_6$ ,  $-S(O)_nR_5$ ,  $-OPO(OR_5)OR_6$ ,  $-PO(OR_5)R_6$ ,  $-OC(O)OR_5$ ,  $-OR_5NR_5R_6$ ,  $-OC(O)NR_5R_6$ ,  $-C(O)NR_5OR_6$ ,  $-COOR_5$ ,  $-SO_3H$ ,  $-NR_5R_6$ ,  $-N[(CH_2)_2]_2NR_5$ ,  $-NR_5COR_6$ ,  $-NR_5COOR_6$ ,  $SO_2NR_5R_6$ ,  $-NO_2$ ,  $-N(R_5)SO_2R_6$ ,  $-NR_5CONR_5R_6$ ,  $-NR_5C(=NR_6)NR_5R_6$ ,  $-NR_5C(=NR_6)N(SO_2R_5)R_6$ ,  $-NR_5C(=NR_6)N(C=OR_5)R_6$ ,  $-tetrazol-5-yl$ ,  $-SO_2NHCN$ ,  $-SO_2NHCONR_5R_6$ , phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

the 5-10 membered cycloheteroalkyl ring formed by  $R_1$  and  $R_2$  together with the carbon atom to which they are attached is



wherein each instance of K is, independently, O, S or  $NR_4$ ;

$R_3$  is alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms having 1 to 3 double bonds, alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl, aryl of 6 to 10 carbon atoms, 5-6 membered heteroaryl

having 1-3 heteroatoms selected from N, NR<sub>4</sub>, O, and S; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl of R<sub>3</sub> may optionally be substituted on any atom cable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds, alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, -OR<sub>5</sub>, =O, -CN, -COR<sub>5</sub>, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, -CONR<sub>5</sub>R<sub>6</sub>, -S(O)<sub>n</sub>R<sub>5</sub>, -OPO(OR<sub>5</sub>)OR<sub>6</sub>, -PO(OR<sub>5</sub>)R<sub>6</sub>, -OC(O)OR<sub>5</sub>, -OR<sub>5</sub>NR<sub>5</sub>R<sub>6</sub>, -OC(O)NR<sub>5</sub>R<sub>6</sub>, -C(O)NR<sub>5</sub>OR<sub>6</sub>, -COOR<sub>5</sub>, -SO<sub>3</sub>H, -NR<sub>5</sub>R<sub>6</sub>, -N[(CH<sub>2</sub>)<sub>2</sub>]<sub>2</sub>NR<sub>5</sub>, -NR<sub>5</sub>COR<sub>6</sub>, -NR<sub>5</sub>COOR<sub>6</sub>, SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, -NO<sub>2</sub>, -N(R<sub>5</sub>)SO<sub>2</sub>R<sub>6</sub>, -NR<sub>5</sub>CONR<sub>5</sub>R<sub>6</sub>, -NR<sub>5</sub>C(=NR<sub>6</sub>)NR<sub>5</sub>R<sub>6</sub>, -NR<sub>5</sub>C(=NR<sub>6</sub>)N(SO<sub>2</sub>R<sub>5</sub>)R<sub>6</sub>, -NR<sub>5</sub>C(=NR<sub>6</sub>)N(C=OR<sub>5</sub>)R<sub>6</sub>, -tetrazol-5-yl, SO<sub>2</sub>NHCN, -SO<sub>2</sub>NHCONR<sub>5</sub>R<sub>6</sub>, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R<sub>4</sub> is hydrogen; aryl; aralkyl, heteroaryl; heteroaralkyl, alkyl of 1-6 carbon atoms; cycloalkyl of 3-6 carbon atoms; -C(O)<sub>n</sub>R<sub>5</sub>, -CONR<sub>5</sub>R<sub>6</sub>, or SO<sub>2</sub>R<sub>5</sub>;

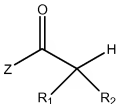
R<sub>5</sub> and R<sub>6</sub> are each independently hydrogen, optionally substituted aryl; 4-8 membered heteroaryl having 1-3 heteroatoms selected from N, NR<sub>4</sub>, O and S; cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms or alkynyl of 2-18 carbon atoms; or R<sub>5</sub> and R<sub>6</sub> taken together with the nitrogen atom to which they are attached may form a 5-10 membered cycloheteroalkyl ring; and n is 1 or 2; or a pharmaceutical salt thereof,

wherein said compound of formula V is made by a method which comprises reacting a sulfonyl fluoride of the formula III



III

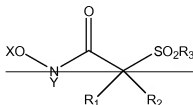
wherein R<sub>3</sub>' is as hereinabove defined for R<sub>3</sub> with the proviso that R<sub>3</sub>' does not contain a group that can form an anion under basic conditions; with a carbonyl compound of the formula IV:



IV

wherein Z is H, OH, YNOX,  $-NR_5R_6$  or  $OR_5$ , and X, Y,  $R_1$ ,  $R_2$ ,  $R_5$ , and  $R_6$  are as hereinabove defined; in the presence of a metal hydride or amide base in an ether organic solvent ~~at temperatures at a temperature of~~ from about  $-78^{\circ}C$  to about  $30^{\circ}C$  to produce an alpha-sulfonyl carbonyl compound of formula V;  
any reactive substituent group(s) being protected during the reaction and removed thereafter; ~~and further if desired isolating any chiral or stereoisomeric product as an individual isomer.~~

2. **(Currently amended)** The method as claimed in claim 1 ~~in which the compound of formula (V) prepared~~ wherein Z is H, OH,  $-NR_5R_6$  or  $OR_{5_2}$  ~~is further reacted to convert it to an alpha-sulfonyl hydroxamic acid derivative of the formula I:~~

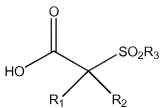


~~wherein X, Y,  $R_1$ ,  $R_2$  and  $R_3$  are as defined in claim 1 or a pharmaceutically acceptable salt thereof; any reactive substituent group(s) being protected during the reaction and removed thereafter; and further if desired isolating any chiral or stereoisomeric product as an individual isomer.~~

3. **(Currently amended)** The method as claimed in Claim 2 wherein Z in the compound of formula V prepared is:

(i)  $OR_5$  wherein  $R_5$  is other than hydrogen and the conversion to the alpha-sulfonyl hydroxamic acid derivative of the formula I is carried out by:

a) reacting the compound of formula V with an alkali metal hydroxide in the presence of water, and/or ether organic solvent or alcohol ~~at temperatures ranging at a temperature of~~ from about  $0^{\circ}C$  to about  $100^{\circ}C$  to produce a carboxylic acid of the formula VI:



wherein, R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub> are as hereinabove defined; and

b) reacting the carboxylic acid of formula VI with a hydroxylamine or hydroxylamine derivative of the formula VII:



**VII**

wherein X and Y are as hereinabove defined; in the presence of suitable coupling reagent and polar organic solvent to produce a hydroxamate of the formula I

or

(ii) OH and the conversion to the alpha-sulfonyl hydroxamic acid derivative of the formula I is carried out according to step b) above.

4. **(Previously presented)** The method of Claim 3 wherein the ether organic solvent in step a) is selected from the group consisting of tetrahydrofuran, diethylether and dioxane.

5. **(Previously presented)** The method of Claim 3 wherein the alcohol in step a) is selected from the group consisting of methanol and ethanol.

6. **(Previously presented)** The method of Claim 3 wherein the alkali metal hydroxide in step a) is selected from the group consisting of lithium hydroxide and sodium hydroxide.

7. **(Original)** The method of Claim 3 wherein the polar organic solvent in step b) is dimethylformamide.

8. **(Previously presented)** The method of Claim 3 wherein the coupling reagent is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, N-hydroxybenzotriazole, N-methylmorpholine oxalylchloride and triethylamine.

9. **(Original)** The method of Claim 3 wherein the coupling reaction is carried out at a temperature from about 0°C to 30°C.

10. **(Previously presented)** The method of Claim 3 wherein the ether organic solvent used in the reaction between the compounds of formula III and IV is selected from the group consisting of tetrahydrofuran, diethylether and dioxane.

11. **(Currently amended)** The method of Claim 3 wherein the metal hydride base or amide base used in the reaction between the compounds of formula III and IV ~~and~~ is selected from the group consisting of lithium ~~diisopropylamine~~ diisopropylamide, lithiumhexamethyldisilazide, and sodium hydride.

12. **(Original)** The method of Claim 1 wherein the sulfonyl fluoride of formula III is prepared by reacting a sulfonyl chloride of the formula II



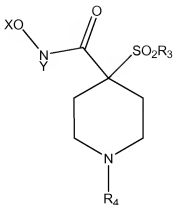
wherein R<sub>3</sub>' is as defined for R<sub>3</sub> in claim 1 with the proviso that R<sub>3</sub>' does not contain a group that can form an anion under basic conditions, with a fluorinating agent in the presence of a polar organic solvent from about 15°C to about 30°C.

13. **(Previously presented)** The method of Claim 12 wherein the fluorinating agent is selected from the group consisting of potassium fluoride, potassium fluoride-calcium fluoride mixture and cesium fluoride.

14. **(Previously presented)** The method of Claim 12 wherein the polar organic solvent is selected from the group consisting of acetonitrile and tetrahydrofuran.

15 – 28. **(Canceled)**

29. **(Currently amended)** The method of Claim 1 wherein X is H or ~~lower~~ alkyl of 1-6 carbon atoms.
30. **(Original)** The method of Claim 1 wherein Y is H.
31. **(Original)** The method of Claim 1 where Z is OH or OR<sub>5</sub> where R<sub>5</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl.
32. **(Canceled)**
33. **(Previously presented)** The method of Claim 1 wherein the cycloheteroalkyl ring is saturated.
34. **(Previously presented)** The method of Claim 1 wherein the cycloheteroalkyl ring has 6 atoms.
35. **(Previously presented)** The method of Claim 1 wherein the heteroatom is NR<sub>4</sub> and R<sub>4</sub> is hydrogen, trifluoromethylsulfonyl, optionally substituted aralkyl of 7-10 carbon atoms, (C<sub>6</sub>-C<sub>10</sub>-aryl)carbonyl-, cycloheteroalkyl-carbonyl or heteroaryl-carbonyl.
36. **(Original)** The method of Claim 1 wherein R<sub>3</sub> is an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group.
37. **(Original)** The method of Claim 1 wherein R<sub>3</sub> is a phenyl group substituted by one or more OR<sub>5</sub> groups.
38. **(Original)** The method of Claim 1 wherein R<sub>5</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl or halophenyl.
39. **(Previously presented)** The method of Claim 1 in which the compound prepared is an alpha-sulfonyl hydroxamic acid derivative of the general formula IA:



**IA**

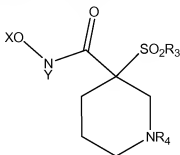
wherein

X is hydrogen, or alkyl of 1-6 carbon atoms; and Y,  $R_3$  and  $R_4$  are as defined in Claim 1 or a pharmaceutically acceptable salt thereof.

40-44. **(Canceled)**

45. **(Original)**

A compound of Formula IX



**IX**

wherein

X is hydrogen, or alkyl of 1-6 carbon atoms;

Y is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6 to 10 carbon atoms, 5-10 membered heteroaryl having 1-3 heteroatoms selected from N,  $NR_4$ , O and S, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl; wherein said alkyl, aryl, heteroaryl, cycloalkyl and cycloheteroalkyl group of Y is optionally substituted on any atom capable of substitution, with 1 to 3 substituents selected from the group consisting of halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms

having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms,  $-\text{OR}_5$ ,  $=\text{O}$ ,  $-\text{CN}$ ,  $-\text{COR}_5$ , perfluoroalkyl of 1-4 carbon atoms,  $-\text{O}$ -perfluoroalkyl of 1-4 carbon atoms,  $-\text{CONR}_5\text{R}_6$ ,  $-\text{S}(\text{O})_n\text{R}_5$ ,  $-\text{OPO}(\text{OR}_5)\text{OR}_6$ ,  $-\text{PO}(\text{OR}_5)\text{R}_6$ ,  $-\text{OC}(\text{O})\text{OR}_5$ ,  $-\text{OR}_5\text{NR}_5\text{R}_6$ ,  $-\text{OC}(\text{O})\text{NR}_5\text{R}_6$ ,  $-\text{C}(\text{O})\text{NR}_5\text{OR}_6$ ,  $-\text{COOR}_5$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{NR}_5\text{R}_6$ ,  $-\text{N}[(\text{CH}_2)_2]_2\text{NR}_5$ ,  $-\text{NR}_5\text{COR}_6$ ,  $-\text{NR}_5\text{COOR}_6$ ,  $\text{SO}_2\text{NR}_5\text{R}_6$ ,  $-\text{NO}_2$ ,  $-\text{N}(\text{R}_5)\text{SO}_2\text{R}_6$ ,  $-\text{NR}_5\text{CONR}_5\text{R}_6$ ,  $-\text{NR}_5\text{C}(=\text{NR}_6)\text{NR}_5\text{R}_6$ ,  $-\text{NR}_5\text{C}(=\text{NR}_6)\text{N}(\text{SO}_2\text{R}_5)\text{R}_6$ ,  $-\text{NR}_5\text{C}(=\text{NR}_6)\text{N}(\text{C}=\text{OR}_5)\text{R}_6$ ,  $-\text{tetrazol-5-yl}$ ,  $-\text{SO}_2\text{NHCN}$ ,  $-\text{SO}_2\text{NHCONR}_5\text{R}_6$ , phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

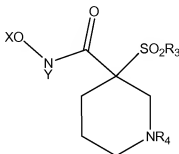
$\text{R}_3$  is alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms having 1 to 3 double bonds, alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl, aryl of 6 to 10 carbon atoms, 5-6 membered heteroaryl having 1-3 heteroatoms selected from N,  $\text{NR}_4$ , O, and S; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl of  $\text{R}_3$  may optionally be substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms,  $-\text{OR}_5$ ,  $=\text{O}$ ,  $-\text{CN}$ ,  $-\text{COR}_5$ , perfluoroalkyl of 1-4 carbon atoms,  $-\text{O}$ -perfluoroalkyl of 1-4 carbon atoms,  $-\text{CONR}_5\text{R}_6$ ,  $-\text{S}(\text{O})_n\text{R}_5$ ,  $-\text{OPO}(\text{OR}_5)\text{OR}_6$ ,  $-\text{PO}(\text{OR}_5)\text{R}_6$ ,  $-\text{OC}(\text{O})\text{OR}_5$ ,  $-\text{OR}_5\text{NR}_5\text{R}_6$ ,  $-\text{OC}(\text{O})\text{NR}_5\text{R}_6$ ,  $-\text{C}(\text{O})\text{NR}_5\text{OR}_6$ ,  $-\text{COOR}_5$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{NR}_5\text{R}_6$ ,  $-\text{N}[(\text{CH}_2)_2]_2\text{NR}_5$ ,  $-\text{NR}_5\text{COR}_6$ ,  $-\text{NR}_5\text{COOR}_6$ ,  $\text{SO}_2\text{NR}_5\text{R}_6$ ,  $-\text{NO}_2$ ,  $-\text{N}(\text{R}_5)\text{SO}_2\text{R}_6$ ,  $-\text{NR}_5\text{CONR}_5\text{R}_6$ ,  $-\text{NR}_5\text{C}(=\text{NR}_6)\text{NR}_5\text{R}_6$ ,  $-\text{NR}_5\text{C}(=\text{NR}_6)\text{N}(\text{SO}_2\text{R}_5)\text{R}_6$ ,  $-\text{NR}_5\text{C}(=\text{NR}_6)\text{N}(\text{C}=\text{OR}_5)\text{R}_6$ ,  $-\text{tetrazol-5-yl}$ ,  $-\text{SO}_2\text{NHCN}$ ,  $-\text{SO}_2\text{NHCONR}_5\text{R}_6$ , phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

$\text{R}_4$  is hydrogen; aryl; aralkyl, heteroaryl; heteroaralkyl, alkyl of 1-6 carbon atoms; cycloalkyl of 3-6 carbon atoms;  $-\text{C}(\text{O})_n\text{R}_5$ ,  $\text{CONR}_5\text{R}_6$  or  $\text{SO}_2\text{R}_5$ ;

$\text{R}_5$  and  $\text{R}_6$  are each independently hydrogen, optionally substituted aryl; 4-8 membered heteroaryl having 1-3 heteroatoms selected from N,  $\text{NR}_4$ , O and S; cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms or alkynyl of 2-18 carbon atoms; or  $\text{R}_5$  and  $\text{R}_6$  taken together with the nitrogen atom to which they are attached may form a 5-10 membered cycloheteroalkyl ring; and  $n$  is 1 or 2; or an optical isomer thereof or a pharmaceutically acceptable salt thereof.

46. **(Previously presented)** The compound according to Claim 45 which is 1-benzyl-3-(4-methoxy-benzenesulfonyl)piperidine-3-carboxylic acid hydroxamide.

47. **(Currently amended)** A pharmaceutical composition comprising [[a]] the compound of Formula IX



IX

as defined in claim 45 or the compound of claim 46 or a pharmaceutically acceptable salt thereof;  
and a pharmaceutically acceptable carrier.

48. **(Currently amended)** A method of treating a pathological condition or disorder responsive to inhibition of inhibiting pathological changes mediated by a TNF-alpha converting enzymes enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 45, or a pharmaceutically acceptable salt thereof.

49. **(Currently amended)** The method of Claim 48 wherein the condition or disorder treated is rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.

50-52. **(Canceled)**

53. **(Previously presented)** The method according to claim 38 wherein R<sub>5</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>2</sub>-C<sub>6</sub> alkynyl.